CHEMISTRY 2600

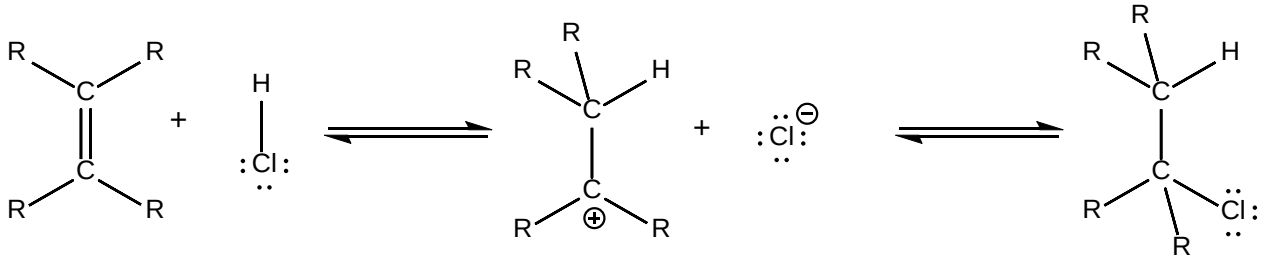
Topic #6: Addition Reactions of Carbonyl Groups

Fall 2018

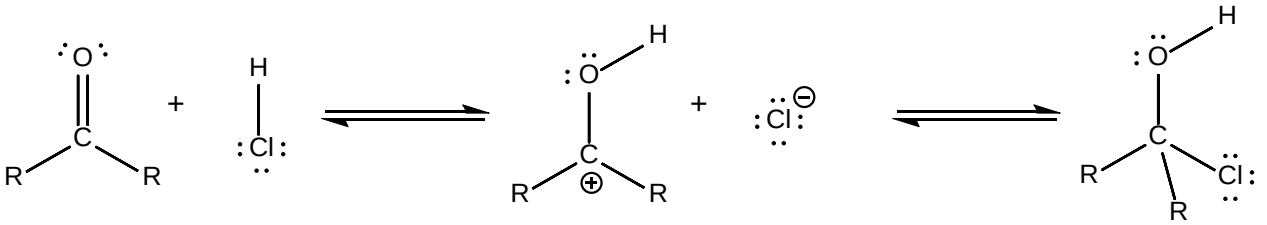
Dr. Susan Findlay

Electrophilic Addition to Carbonyl Groups

- In Chapter 9, we saw that water, HCl, HBr and HI could be added across the C=C of an alkene. This is an equilibrium reaction for which the equilibrium favours the products.



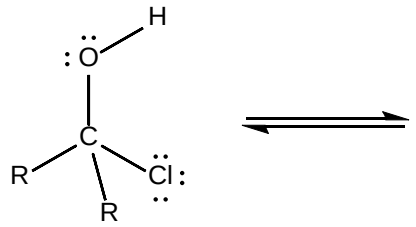
- These small molecules can be added across C=O via the same mechanism; however, this equilibrium favours the reactants.

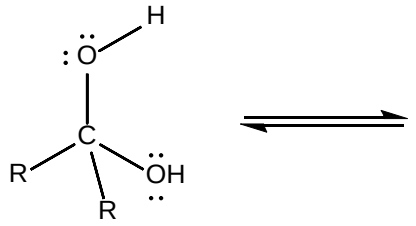


- What causes this difference in reactivity?

Electrophilic Addition to Carbonyl Groups

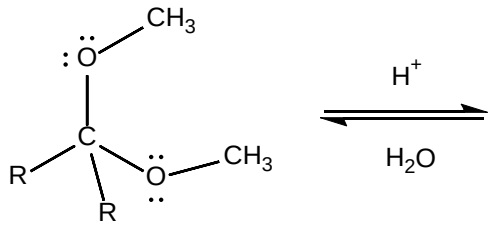
- Because electrophilic addition to a carbonyl group is reactant-favoured, whenever we see a *gem*-diol (two –OH groups on one carbon) or a carbon atom with a –OH group and a halogen attached, we expect it to collapse to give a carbonyl group:





Electrophilic Addition to Carbonyl Groups

- Similarly, a carbon atom with two alkoxy groups attached (an **acetal** or **ketal**) will collapse to a carbonyl group in the presence of aqueous acid:

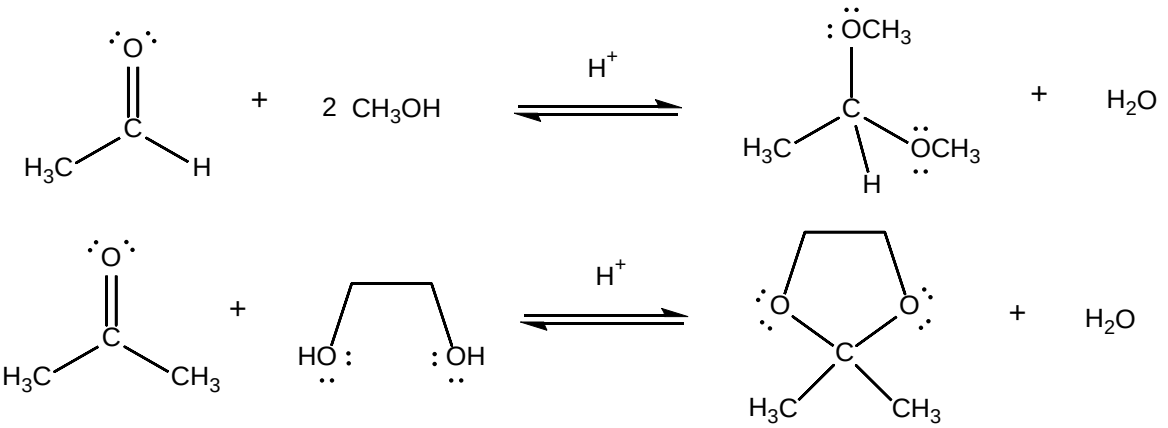


- Unlike the molecules on the previous page, acetals and ketals are stable in aqueous base. They won't collapse to carbonyl groups except in the presence of acid and water. This is very useful...

Electrophilic Addition to Carbonyl Groups

- By controlling the reaction conditions, we can favour formation of an acetal (from an aldehyde) or ketal (from a ketone):

e.g.

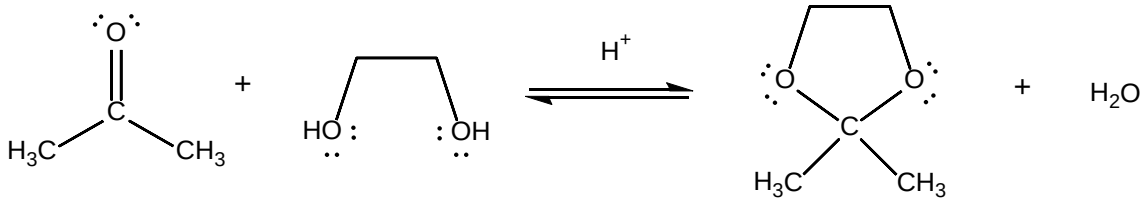


How would you promote the forward reaction?

- So, what we have is a reaction that we can use to:
  - First, “protect” a carbonyl group as a less reactive species.
  - Second, do some reaction *(on another part of our molecule)* that would have been incompatible with the carbonyl group.
  - Third, remove the “protecting group” to recover the carbonyl group (in this case, by adding aqueous acid, as on the previous page)

Electrophilic Addition to Carbonyl Groups

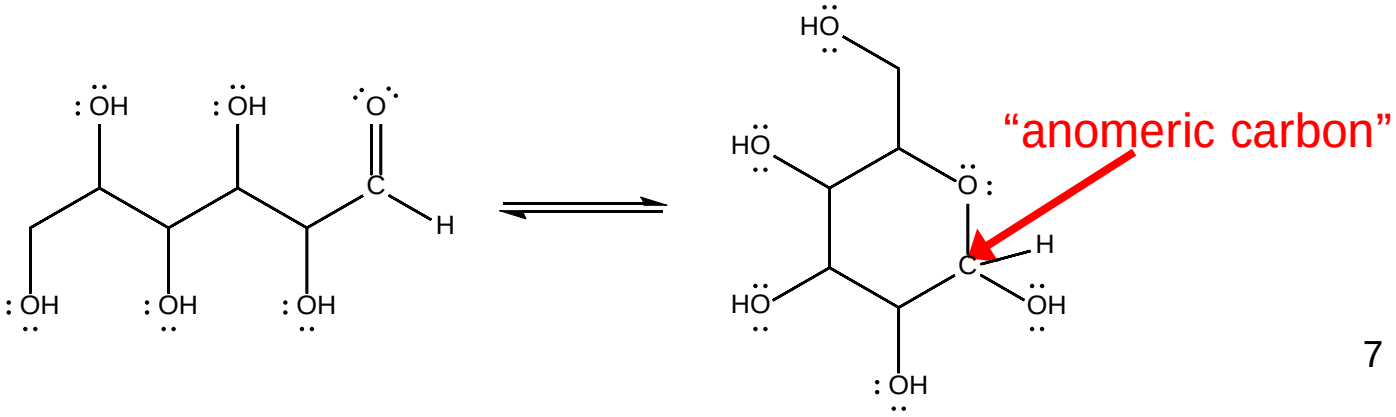
- What is the mechanism for the following reaction “protecting” a ketone as a ketal?



Electrophilic Addition to Carbonyl Groups

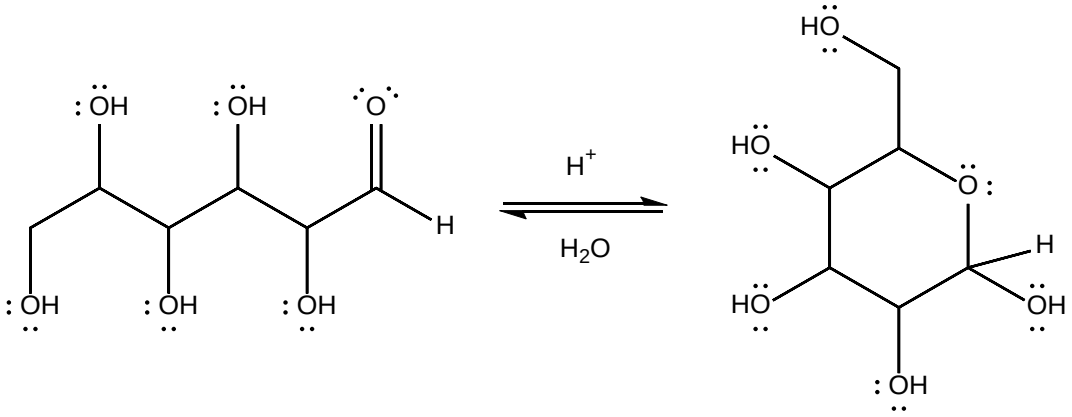
- While most electrophilic addition reactions to carbonyls aren't product-favoured (without careful consideration of the reaction conditions), there is a very important exception to this rule.
- Sugars are polyhydroxyketones or polyhydroxyaldehydes <u>but</u> the carbonyl group isn't immediately obvious because an electrophilic addition reaction occurs in the presence of aqueous acid, forming a stable 5- or 6-atom ring.

  e.g. The polyhydroxyaldehyde below could be glucose *(or galactose or any number of other sugars, depending on the stereochemistry).* It exists primarily in the cyclic form shown (a **hemiacetal**, literally a "half acetal").



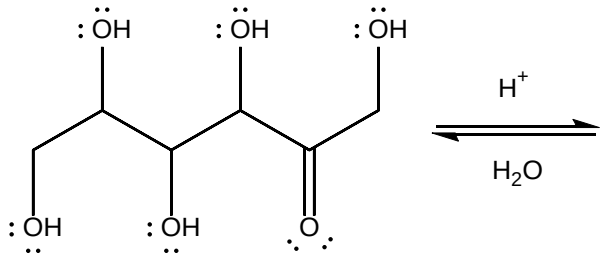
Electrophilic Addition to Carbonyl Groups

- Propose a mechanism for the equilibrium reaction converting linear glucose to the hemiacetal form in dilute aqueous acid.



Electrophilic Addition to Carbonyl Groups

- Fructose occurs naturally as a mixture of two hemiacetals – one with a 5-atom ring (the “furanose” form) and one with a 6-atom ring (the “pyranose” form). The linear form of fructose is shown below – again, without the stereochemistry. Draw the structures of <u>both</u> hemiacetal forms of fructose.



Nucleophilic Addition to Carbonyl Groups

- While carbonyl groups can undergo some electrophilic addition reactions, the vast majority of additions to carbonyls are **nucleophilic additions**.
- In a nucleophilic addition reaction, a nucleophile attacks the electrophilic carbon atom of the carbonyl group, breaking the C-O π bond and transferring that electron pair onto the O.

- If there is a leaving group attached to the carbonyl group, a lone pair on the oxygen atom will then re-form the C-O π bond, kicking out the leaving group. This will be the case for esters, anhydrides, acid chlorides, etc. *(as you've seen in lab)*

Nucleophilic Addition to Carbonyl Groups

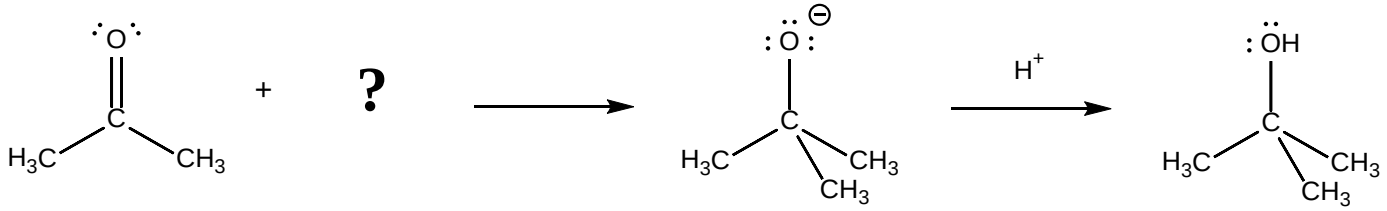
- Nucleophilic additions to carbonyl groups are particularly important as they allow us to form new carbon-carbon bonds. We've seen a few ways to do this so far (in CHEM 2500 too):

But few are as flexible as nucleophilic addition to a carbonyl.

Nucleophilic Addition to Carbonyl Groups

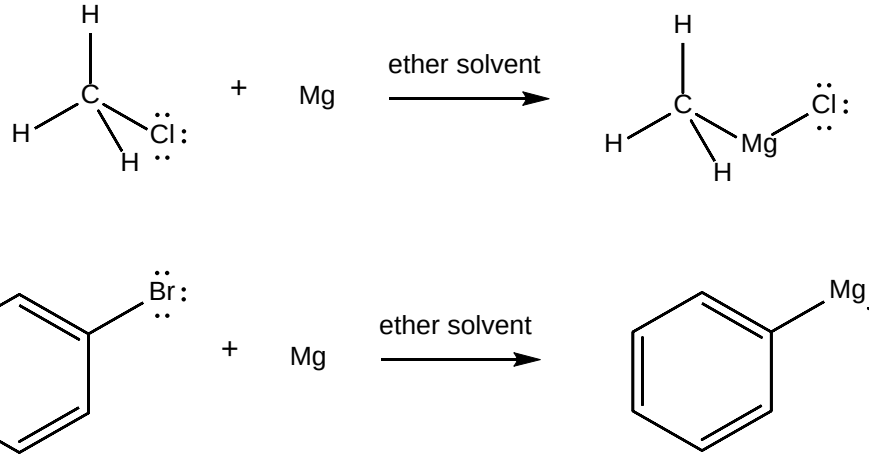
- What's so special about this class of reaction?
  - We aren't limited to forming rings.
  - We can make a wide variety of carbonyl groups (from alcohols, alkenes, alkynes, etc.).
  - We can make a wide variety of carbon-containing nucleophiles (from alkynes, haloalkanes, ketones/aldehydes, etc.).

- Imagine that you wanted to make *tert*-butanol via a nucleophilic addition to acetone. What nucleophile would you need?



Nuc. Add'n to C=O w/ Grignard Reagents

- Clearly, this nucleophile can't be made by deprotonating an alkane! So, how to make it?
- François Auguste Victor Grignard solved this problem (earning himself a Nobel Prize in 1912) by adding magnesium to organic compounds containing C-Cl, C-Br or C-I bonds. A magnesium atom inserts between the carbon and halogen atoms, making something that acts like it has a negatively charged carbon atom!

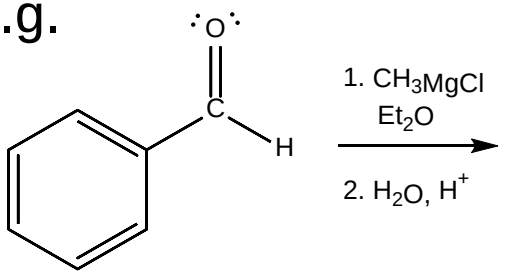


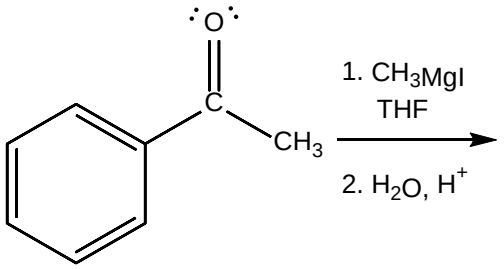
- The products of these reactions are called **Grignard reagents**, and they are excellent nucleophiles *(as well as excellent bases)*.

Nuc. Add'n to C=O w/ Grignard Reagents

- Grignard reagents react readily with a variety of electrophiles containing C-X pi bonds (where X = O, N, S, etc.) They **do not**, however, do S_N2 reactions with alkyl halides.

  e.g.

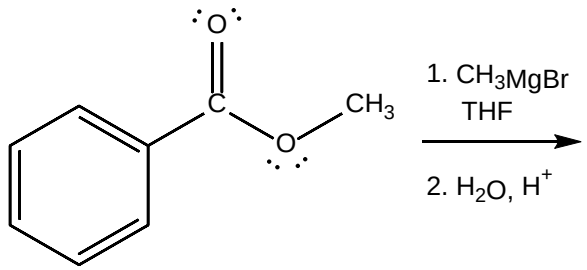




- What happens if water gets into step #1 of either reaction?

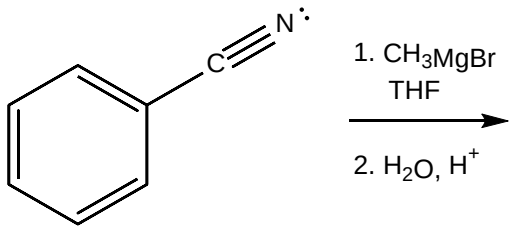
Nuc. Add'n to C=O w/ Grignard Reagents

- What happens if we use an ester instead of an aldehyde or ketone?



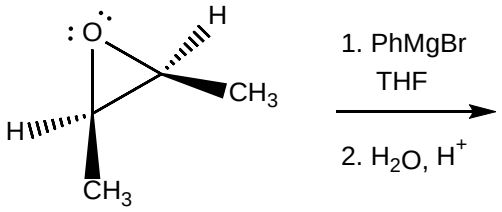
Nuc. Add'n to C=O w/ Grignard Reagents

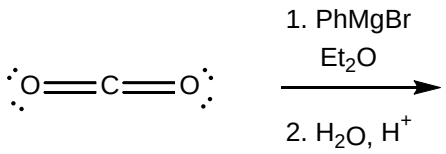
- We can solve that problem by using a nitrile instead:



Nuc. Add'n to C=O w/ Grignard Reagents

- Grignard reagents will even react with epoxides and with CO_2:





...but remember that they DON'T react with alkyl halides!

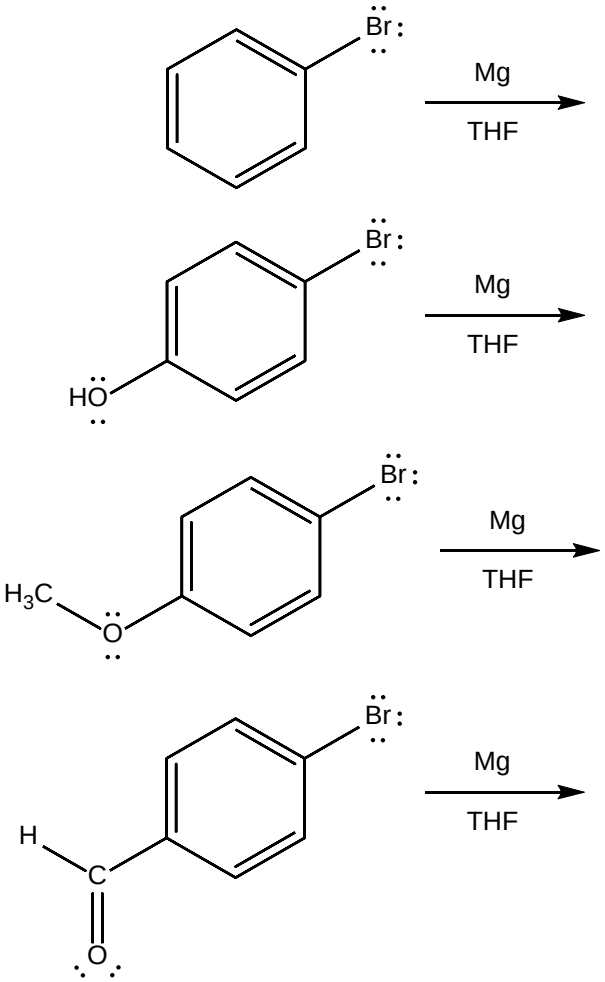
Nuc. Add'n to C=O w/ Grignard Reagents

- Grignard reagents are exceptionally strong bases which will react with any hydrogens that are at all acidic.
- This can be taken advantage of to produce a Grignard reagent from a terminal alkyne:

- While very useful, the high reactivity of Grignard reagents limits which ones can be prepared.
  - It is **not** possible to prepare a Grignard reagent in the presence of any hydrogen atom that is at all acidic – including any hydrogen atom bonded to a heteroatom! *(No NH, OH, SH, etc. allowed.)*
  - It is **not** possible to prepare a Grignard reagent in the presence of any good electrophile. *(The Grignard reagent is always mixed with the ketone, aldehyde, ester, nitrile, epoxide, etc. after it's prepared.)*

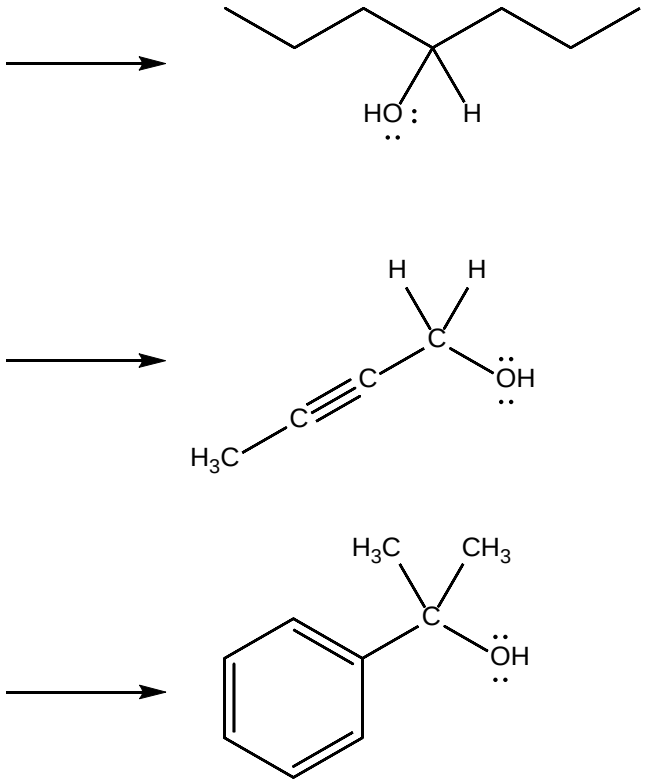
Nuc. Add'n to C=O w/ Grignard Reagents

- Which of the following aromatic bromides can be converted into a Grignard reagent? For those that can, show the product.



Nuc. Add'n to C=O w/ Grignard Reagents

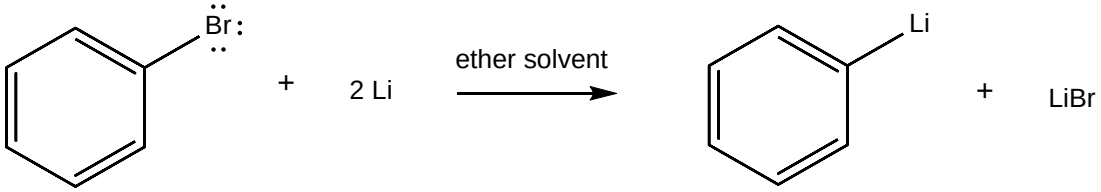
- How would you prepare each of the following alcohols by from a carbonyl group and Grignard reagent(s)?



- These are more example of **retrosynthesis**.

Nuc. Add'n to C=O w/ Alkyllithium Reagents

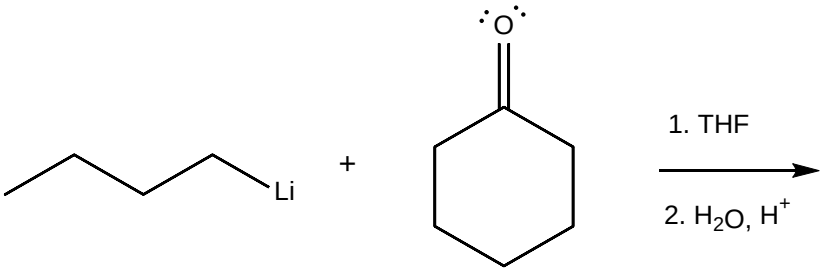
- Alkyllithium reagents can be prepared using lithium instead of magnesium:

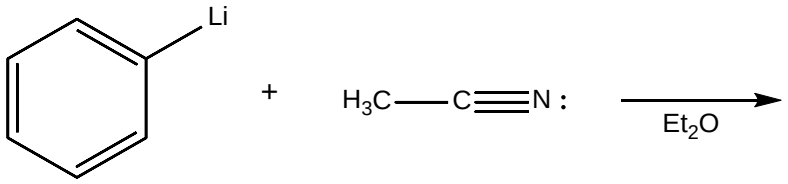


- Because lithium is even less electronegative than magnesium, alkyllithium reagents are even more nucleophilic and even more basic than Grignard reagents.
- *n*-Butyllithium and *t*-butyllithium are often used to remove hydrogen atoms you really wouldn't consider to be particularly acidic – such as the hydrogen atoms on a benzene ring! Not all that surprising when you consider that the pK_a values for their conjugate acids (butane and 2-methylpropane) are ~50!!!

Nuc. Add'n to C=O w/ Alkyllithium Reagents

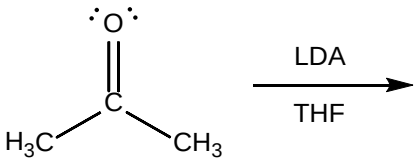
- Alkyllithium reagents react with carbonyl groups, epoxides, nitriles, etc. in the same way that Grignard reagents do.





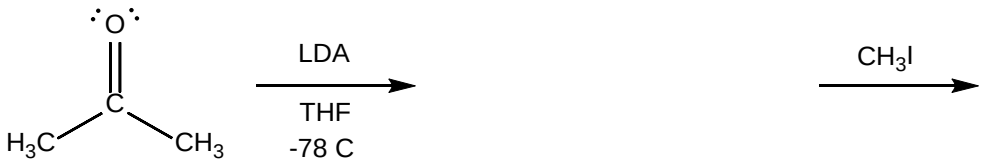
Nuc. Add'n to C=O w/ Enolates ("Aldol Rxn")

- One other important class of nucleophilic carbon atom is the **enolate** (the conjugate base of an enol). In CHEM 2500, you saw that the hydrogen atom α to a carbonyl group was quite acidic (pK_a typically 20-25):



- This generates a nucleophilic carbon atom that can be used in both S_N2 reactions and nucleophilic addition reactions.

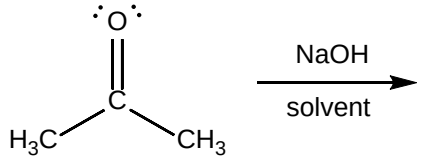
e.g.



Reaction conditions must be carefully controlled to prevent addition of a second alkyl group.

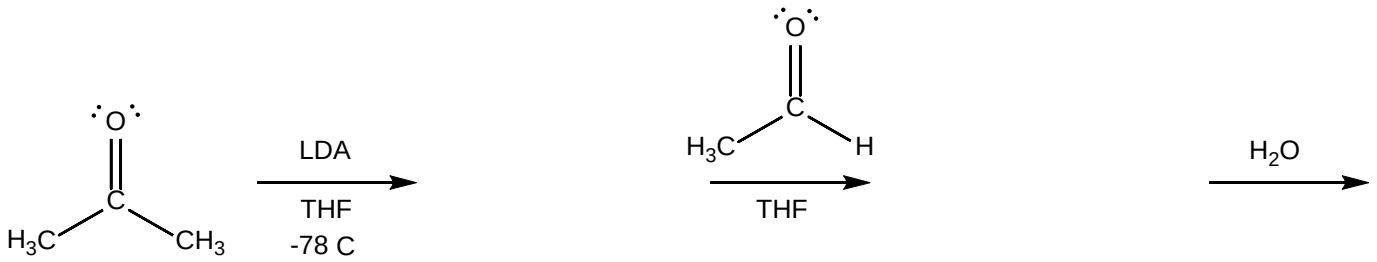
Nuc. Add'n to C=O w/ Enolates ("Aldol Rxn")

- This chemistry is the reason why heating acetone with a small amount of moderate-to-strong base (NaOH or stronger) results in a tarry mess. Consider what happens when no external electrophile is added, leaving neutral acetone molecules as the only available electrophiles:



Nuc. Add'n to C=O w/ Enolates ("Aldol Rxn")

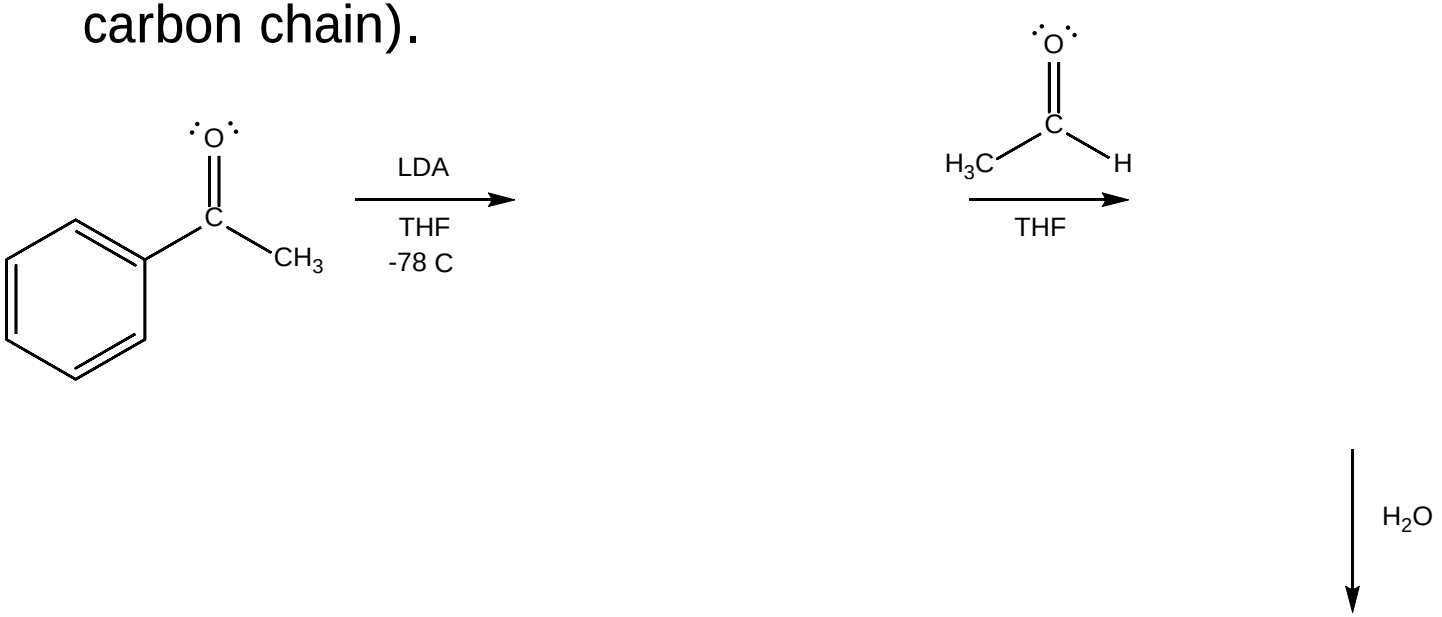
- While the reaction on the previous page isn't hugely useful, this chemistry can be put to good use with some careful planning:
  - We make sure that we use an excess of a strong enough base that the enolate forms 100%, leaving no electrophilic ketone or aldehyde. This often means using low temperatures while making the enolate.
  - Once the enolate has completely formed, we add a reactive electrophile. Aldehydes are more reactive than ketones, so they're usually a better choice.
  - After adding the electrophile, the solution may be allowed to warm.



- And we've extended our carbon chain!

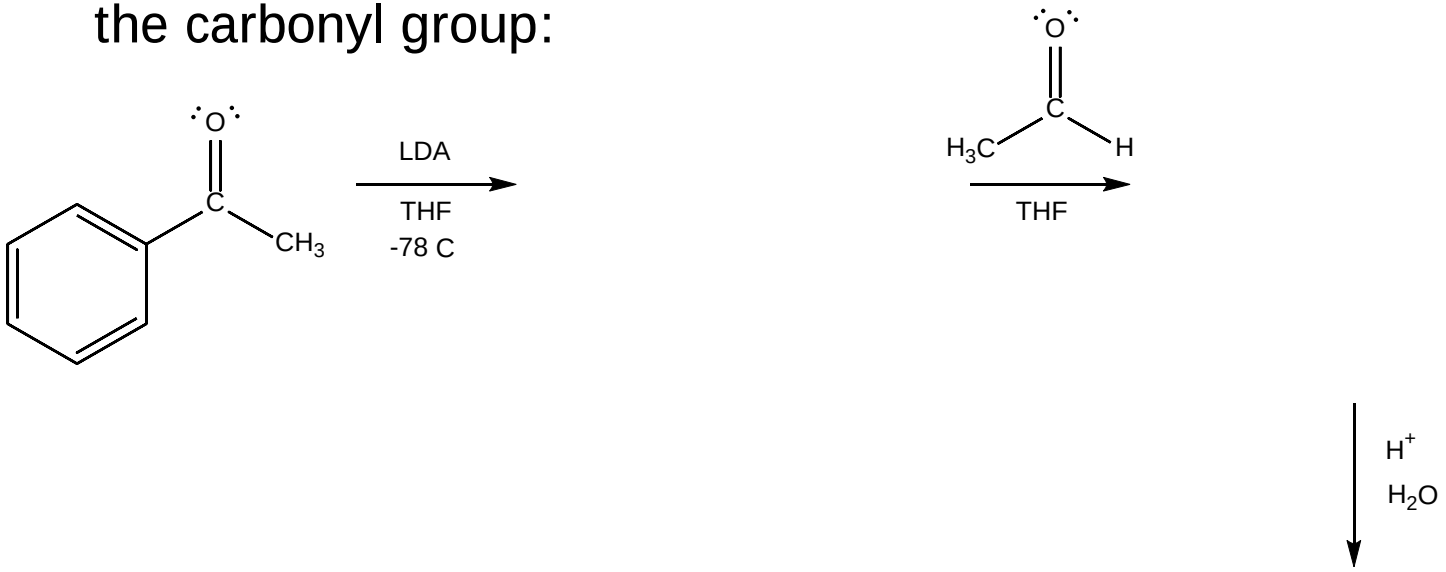
Nuc. Add'n to C=O w/ Enolates ("Aldol Rxn")

- This reaction is known as the **aldol** reaction. It takes an **ald**ehyde and converts it into an alcoh**ol** (while extending the carbon chain).



Nuc. Add'n to C=O w/ Enolates ("Aldol Rxn")

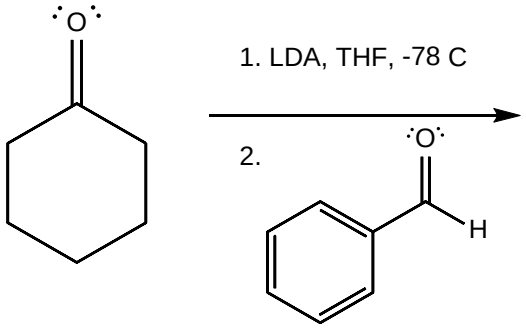
- If an aldol reaction is worked up under acidic conditions, an E2 reaction is likely to follow, giving a double bond conjugated to the carbonyl group:



There is more thought put into work-up conditions than might immediately be apparent from a lab manual... ☺

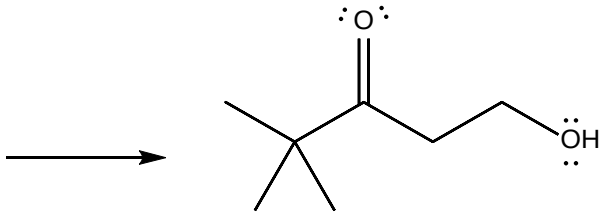
Nuc. Add'n to C=O w/ Enolates ("Aldol Rxn")

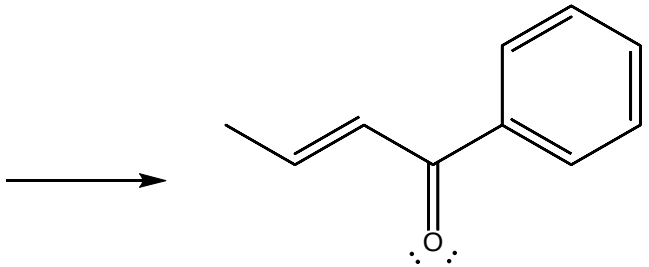
- What are the products of the following aldol reaction with (a) aqueous work-up, or (b) acidic work-up:



Nuc. Add'n to C=O w/ Enolates ("Aldol Rxn")

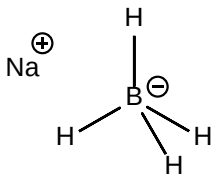
- How would you make the following compounds via aldol reactions?

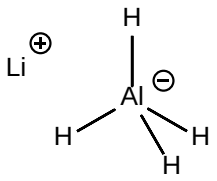




Nuc. Add'n to C=O w/ H^- Equivalents

- Addition of hydride to a carbonyl group (reducing it to an alcohol) is also a very useful reaction. Hydride is H^-; however, we cannot just add H^- to C=O as H^- is much more basic than nucleophilic (giving the enolate where possible). *NaH and KH are great bases!*
- So, how can we make an electron rich, nucleophilic hydrogen atom? Answer: Attach it to a less electronegative element. Boron and aluminium are the usual choices:

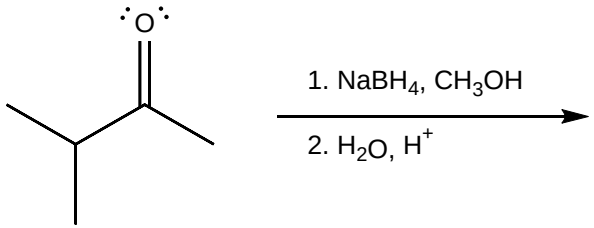


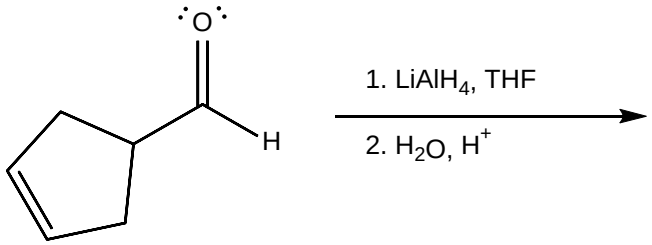


- $LiAlH_4$ is more reactive than $NaBH_4$. Why do you think that is?

Nuc. Add'n to C=O w/ H^- Equivalents

- Both $LiAlH_4$ and $NaBH_4$ will reduce ketones and aldehydes to alcohols:

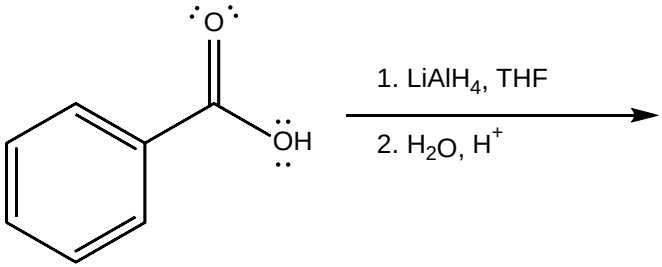


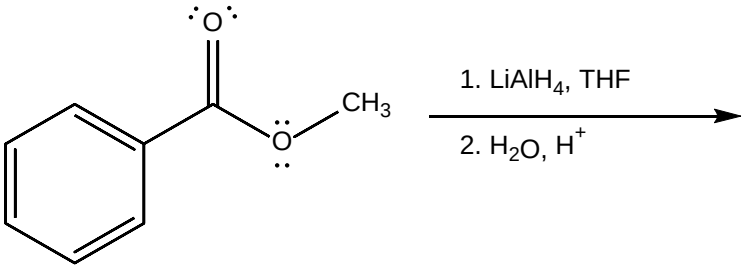


- Neither $LiAlH_4$ nor $NaBH_4$ will react with an alkene. Why not?

Nuc. Add'n to C=O w/ H^- Equivalents

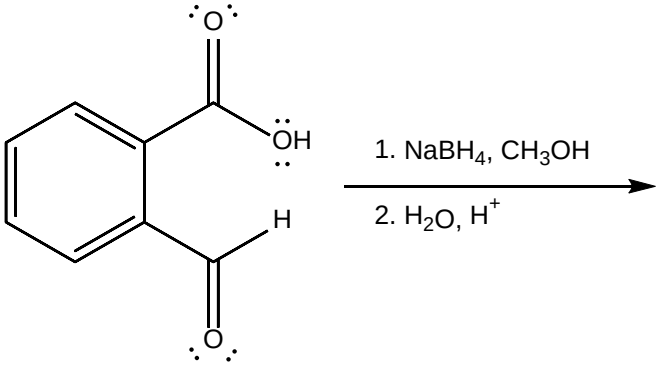
- $LiAlH_4$ can also reduce carboxylic acids and esters to alcohols. $NaBH_4$ will not.

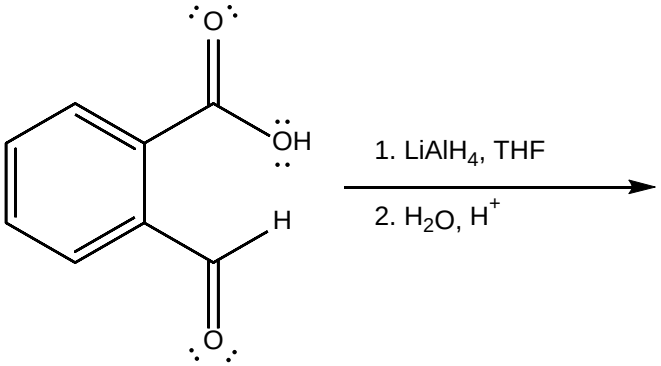




Nuc. Add'n to C=O w/ H^- Equivalents

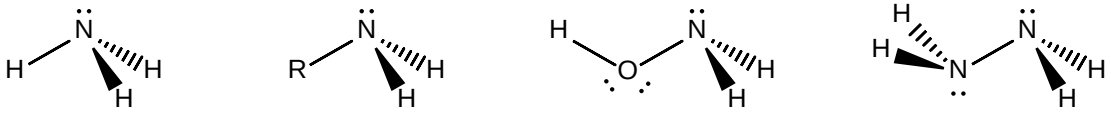
- In this way, $NaBH_4$ can be used to selectively reduce one type of carbonyl group in the presence of another.





Nuc. Add'n to C=O w/ Nitrogen Nucleophiles

- One last group of nucleophiles that can add to carbonyl groups are the amines and related compounds:



- The mechanism for this reaction is very similar to that for addition of water to a carbonyl group; however, because amines are better nucleophiles than alcohols/water, the carbonyl group doesn't have to be protonated first.
- A small amount of acid is necessary to generate a leaving group of water (R-OH_2^+) midway through the mechanism; however, too much acid will prevent the reaction from proceeding. What would happen if you combined a ketone, an amine and a large amount of acid?

Nuc. Add'n to C=O w/ Nitrogen Nucleophiles

- In order to make H^+ available – but not too available – nucleophilic addition of nitrogen to a carbonyl group is usually done at a pH of 6-7. One way to accomplish this is to add the nucleophile as the HCl salt.

  e.g. An aqueous solution of hydroxylamine hydrochloride ($NH_2OH \cdot HCl$) is added to cyclopentanone. What happens?

- The product of this reaction is an **oxime** (C=N-OH)

Nuc. Add'n to C=O w/ Nitrogen Nucleophiles

- Alternately, we can add the nucleophile to a solution of the electrophile in a mixture of alcohol and dilute acid.

  e.g. 2,4-dinitrophenylhydrazine is added to a solution of propanal and dilute acid in ethanol. What happens?

- The product of this reaction is a **hydrazone** ($C=N-NR_2$)

Nuc. Add'n to C=O w/ Nitrogen Nucleophiles

- Propylamine (aka 1-propanamine) is added to a solution of benzaldehyde and dilute acid in ethanol. What happens?

- The product of this reaction is an **imine** (C=N-R).

Nuc. Add'n to C=O w/ Nitrogen Nucleophiles

- The C=N bond is of similar strength to the C=C bond, so the reactions on the previous pages are fairly easily reversed by adding aqueous acid.
- The C=N bond is different from the C=C bond in one important way, though. It is polar, so the carbon atom is still electrophilic. This means that an imine can be reduced to an amine by adding nucleophilic hydrogen (i.e. $LiAlH_4$ or $NaBH_4$):

Nuc. Add'n to C=O w/ Nitrogen Nucleophiles

- Going in the opposite direction, an oxime can be oxidized to a nitrile by heating it with acid (e.g. H_3PO_4). This gives us a way to convert an aldehyde to a nitrile in two steps:

- The reverse process (nitrile to aldehyde) can be accomplished by reducing a nitrile to an imine with $NaBH_4$ then adding $H^+_{(aq)}$.

Wolff-Kischner Reaction

- Another use of nitrogen nucleophiles is to reduce a carbonyl group right down to a CH_2 (or CH_3 if it was an aldehyde). In the Wolff-Kischner reaction, a ketone or aldehyde is heated with hydrazine and aqueous potassium hydroxide:

  - First, the hydrazine reacts with the carbonyl group to make a hydrazone:

Wolff-Kischner Reaction

- Then the base deprotonates the terminal nitrogen, migrating the double bond from C=N to N=N:

- Finally, the base deprotonates the terminal nitrogen again, eliminating nitrogen gas (N_2) and giving a carbanion which is quickly protonated by water:

- This is one way to get rid of a carbonyl group that was useful to assemble a target molecule but is not wanted in the product.